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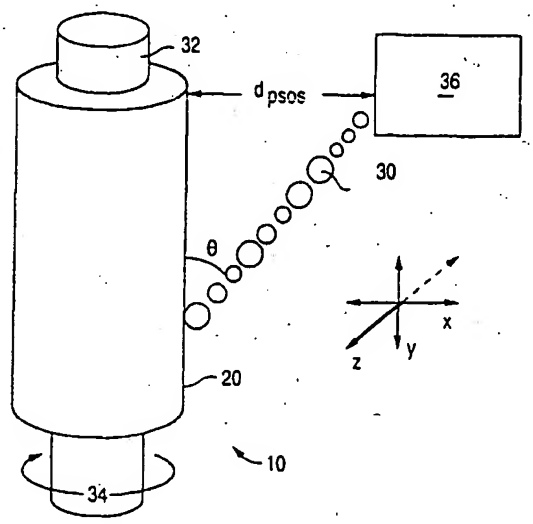
(54) Title: A METHOD OF LOADING A SUBSTANCE ONTO AN IMPLANTABLE DEVICE



(57) Abstract: Methods of loading a substance onto an implantable device are disclosed. The implantable device may be a stent or a graft, with or without depots formed within an outer surface thereof. An exemplary method includes the act of projecting particles of the substance from a pressurized particle source onto a preselected region of the implantable device. An implantable device loaded with a substance in accordance with the method is also provided. The projected particles may be made of any substance or substances suitable for loading onto an implantable device in solid form including, but not limited to, therapeutic substances or agents, radioisotopes, radiopaque substances, polymers, proteins, and nucleic acids. Also provided is a method of loading a substance onto a stent having an outer surface with a plurality of depots formed therein. The method includes the act of projecting particles including the substance from a pressurized particle source onto the outer surface of the stent, wherein the particles are loaded into the plurality of depots. A stent loaded with a substance in accordance with the method is also provided.

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A METHOD OF LOADING A SUBSTANCE ONTO AN IMPLANTABLE DEVICE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to implantable devices, examples of which include stents and grafts. More particularly, the present invention is directed to a method of loading an implantable device with one or more substances.

Description of the Related Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress the atherosclerotic plaque of the lesion against the inner wall of the artery to dilate the lumen. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the vessel after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, an implantable device, examples of which include stents and grafts, may be implanted.

Stents are scaffoldings, usually cylindrical or tubular in shape, which function to physically hold open and, if desired, to expand the wall of the vessel. Typically stents are

solvent-polymer solution. The amount of therapeutic substance that may be loaded onto the implantable device is limited by the solubility of the therapeutic substance in the solvent or solvent-polymer solution.

Another shortcoming of the above-described method for medicating an implantable device is incompatibility with some therapeutic substances. For example, some therapeutic substances are delicate and cannot tolerate processing in the presence of a solvent and/or a polymer for extended periods of time. This is especially true for peptide-type therapeutic substances, which have tertiary structures susceptible to transmutation.

SUMMARY OF THE INVENTION

The present invention provides a method by which implantable devices, such as stents and grafts, may be loaded with therapeutic substances, among other possibilities, such that the burst effect and the transmutation of delicate therapeutic substances are minimized while loading of the substances is maximized.

An exemplary method within the present invention includes the act of projecting a dry stream of particles including a therapeutic substance from a pressurized particle source onto a preselected region of the implantable device.

In some embodiments, the therapeutic substance is selected from antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof. In other embodiments, the substance is a radioactive isotope or a radiopaque substance. In still other embodiments, the substance is a bioabsorbable polymer, a biomolecule, or a biostable polymer.

The preselected region upon which the particles are projected may include the entire outer surface or a portion of the implantable device, such as a portion in a middle section of the implantable device or a portion adjacent an end of the implantable device.

In some embodiments, the outer surface of the implantable device includes a plurality of depots formed therein. In such embodiments, particles may be projected onto a portion of the

Figure 5B illustrates the primered implantable device of Figure 5A, wherein the particles of Figure 3 have adhered to the primer layer.

Figure 5C illustrates the primered implantable device of Figure 5A, wherein the particles of Figure 3 have been embedded in the primer layer.

Figures 6A, 6B, and 6C illustrate various patterns in which the particles of Figure 3 may be loaded onto the outer surface of the implantable device of Figure 1A.

Figure 7A illustrates the stent of Figure 2C, wherein the particles of Figure 3 have been loaded onto the outer surface and within the depot.

Figure 7B illustrates the stent of Figure 7A after surplus particles have been removed from areas other than within the depot.

Figure 8 illustrates the stent of Figure 2C, wherein the particles of Figure 3 have been loaded onto the primered outer surface and within the primered depot.

Figure 9A illustrates the implantable device of Figure 5B after a topcoat has been applied over the particles.

Figure 9B illustrates the implantable device of Figure 7B after a topcoat has been applied over the particles within the depot.

Figure 9C illustrates the implantable device of Figure 7B after a topcoat has been applied along the outer surface and over the particles within the depot.

Figure 9D illustrates the implantable device of Figure 8 after a topcoat has been applied over the particles within the depot and over the particles along the outer surface.

DETAILED DESCRIPTION

The present invention provides methods of loading a substance onto an implantable device, i.e., a device that is designed to be implanted in a human or animal body.

The surface properties of implantable device 10 may vary according to the desired use of implantable device 10. In some embodiments, inner surface 22 and/or outer surface 20 of implantable device 10 is polished via conventional electropolishing techniques, the use of abrasive slurries, or other polishing methods known to those of ordinary skill in the art. In other embodiments, portions of outer surface 20 are roughened via the creation of asperities while inner surface 22 remains smooth. Asperities can be created by projecting a stream of pressurized grit onto outer surface 20. Asperities can also be formed by removing material from outer surface 20, for example, by chemical etching with or without a patterned mask. Alternatively, asperities can be formed by adding material to outer surface 20, for example, by welding powder to outer surface 20 or by sputtering onto outer surface 20.

Figure 2A is a side view of implantable device 10. In Figure 2A, body 12 of implantable device 10 is formed from thread elements 24 engaged to one another by connecting elements 26. However, the underlying structure of implantable device 10 can be of virtually any design.

Figure 2B illustrates the portion of implantable device 10 shown in circle 2B of Figure 2A. Figure 2B shows that thread elements 24 and connecting elements 26 have a plurality of depots 28 formed in outer surface 20. Depots 28, which may also be referred to as pores or cavities, can be formed in virtually any implantable device 10 structure at any preselected location within implantable device 10. The location of depots 28 within implantable device 10 varies according to intended usage and application. Depots 28 may be formed on implantable device 10 by exposing outer surface 20 to an energy discharge from a laser, such as an excimer laser. Alternative methods of forming such depots 28 include, but are not limited to, physical and chemical etching techniques. Such techniques are well-known to one of ordinary skill in the art.

Figure 2C is a cross-sectional view of a single depot 28 of Figure 2B Depot 28 may have any preselected depth d, width w, and geometrical configuration. Depth d and width w of depot 28 typically depend on the material and dimensions of implantable device 10 and the type and amount of substances deposited within depot 28 as well as on the clinical purpose and usage of implantable device 10. Depth d and width w of the individual depots 28 formed on a single implantable device 10 can vary relative to one another. Depot 28 may be formed in a variety of selected geometrical shapes including, but not limited to, generally cylindrical shapes, generally conical shapes, generally round shapes, elongated trenches, and irregular shapes. As discussed

Alternatively, suitable particles 30 of a particular substance may be obtained from a commercial supplier of that substance and used in the present invention with or without modification. Particles 30, particularly when obtained from a commercial supplier, may include extraneous materials, e.g., fillers such as cellulose, in addition to the substance desired to be loaded onto implantable device 10. Such materials should be biocompatible as well as compatible with the substance to be loaded onto implantable device 10, such that the characteristics, effectiveness, and physical structure of the substance is not adversely altered.

While particles 30 themselves are projected in dry, solid form onto implantable device 10, as will be described below, particles 30 may contain trace amounts of a liquid, such as a solvent used during manufacturing or processing of particles 30. In addition, particles 30 may contain some amount of water, particularly if particle 30 is made of a hygroscopic substance, since such substances absorb moisture from the air.

Therapeutic substances that may be used with the present invention include, but are not limited to, antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, antiallergic, antiangiogenic, and angiogenic substances as well as combinations thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g., TAXOTERE from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., ADRIAMYCIN from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., MUTAMYCIN from Bristol-Myers Squibb Co., Stamford, Conn.) Examples of such suitable antiinflammatories include glucocorticoids such as dexamethasone, methylprednisolone, hydrocortisone and betamethasone, superpotent glucocorticoids such as clobustasol, halobetasol, and diflucortolone, and non-steroidal antiinflammatories such as aspirin, indomethacin and ibuprofen. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or antiproliferative agents include actinomycin D as well as derivatives and analogs thereof (manufactured by Sigma-Aldrich, Milwaukee, WI;

lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly (amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. Biomolecules such as heparin, fibrin, fibrinogen, cellulose, starch, and collagen are typically also suitable. A biostable polymer does not break down in the body, and thus a biostable polymer is present in the body for a substantial amount of time after delivery unless some modification is made to allow the polymer to break down. Examples of biostable polymers include, but are not limited to, PARYLENE, PARYLAST, polyurethane (for example, segmented polyurethanes such as BIOSPAN), polyethylene, polyethlyene teraphthalate, ethylene vinyl acetate, silicone, and polyethylene oxide.

In other embodiments, particles 30 may include nucleic acids or proteins. Examples of such nucleic acids include phosphorodiamidate morpholino oligomers (PMO), cyclic-3'-5'-adenosine monophosphate (8-Cl-cAMP), Antisense oligonucleotides, and various nucleic acids encoding for growth factors such as vascular endothelial cell growth factor (VEGF). Examples of proteins include growth factors such as VEGF.

Loading Particles onto an Implantable Device

Prior to projecting particles 30 onto implantable device 10, implantable device 10 should be clean and free from contaminants that may be introduced during manufacturing. Implantable device 10 may optionally be subjected to physical treatments, such as, but not limited to, the creation of depots 28 within outer surface 20 or the polishing of inner surface 22 and/or outer surface 20, as described above.

In embodiments in which inner surface 22 of implantable device 10 has been polished smooth, particular care should be taken to protect inner surface 22 during projection of particles 30 onto outer surface 20. For example, a mandrel or a hypo tube may be inserted within hollow bore 18 of implantable device 10, such that inner surface 22 is shielded from projected particles 30. Alternatively, a balloon may be inserted into hollow bore 18 of implantable device 10 and inflated to prevent particles 30 from striking inner surface 22. Inner surface 22 can also be masked with a temporary protective coating that is removed after particles 30 have been

In some embodiments, mandrel 32 is capable of motion along the x, y, and z axes as well as in the rotational direction 34. Similarly, particle source 36 may be capable of motion along the x, y, and z axes as well as of rotation about implantable device 10, with or without a mandrel inserted therein, in the direction 34.

The method of projecting particles as depicted in Figure 4 and described above may be used to load particles onto a preselected region of implantable device 10 as discussed below.

a. Loading Particles on the Outer Surface of the Implantable Device

In some embodiments, it is desired to load particles 30 along outer surface 20 of implantable device 10. In such embodiments, a polymeric primer 38, may be applied to outer surface 20 of implantable device 10 prior to the projection of particles 30 onto outer surface 20, as depicted in Figure 5A. Primer 38 facilitates retention of particles 30 on outer surface 20. As shown in Figure 5B, particles 30 may adhere to the polymeric material of primer 38 upon impact. Alternatively, particles 30 may become completely or partially embedded in primer 38, as depicted in Figure 5C.

The primer 38 should be biocompatible, including polymers that are non-toxic, non-inflammatory, chemically inert, and substantially non-immunogenic in the applied amounts. Examples of suitable polymers were listed above with reference to polymers of which particle 30 may be made, and such examples are equally applicable here.

Polymeric primer 38 may itself include a therapeutic substance, which may be delivered in combination with the therapeutic substance of particle 30.

Polymeric primer 38 can be applied onto outer surface 20 of implantable device 10 by any conventional method, such as by spraying the polymeric material onto implantable device 10 or immersing implantable device 10 in the polymeric material. Variations of spray and immersion techniques are also suitable methods of applying primer 38 to implantable device 10. In one such variation, primer 38 may be applied by spraying or immersing implantable device 10 as described above. The polymer-coated implantable device 10 is then centrifuged. The rotation of implantable device 10 creates a centrifugal force upon the polymeric material applied to implantable device 10. This centrifugal force causes excess accumulations of the polymer to be more evenly redistributed over implantable device 10 and thus provides a more even, uniform

and 16 of outer surface 20 to load particles 30 at one or both ends 14 and 16 of the primered implantable device 10.

b. Loading Particles into Depots Formed in the Outer Surface of the Implantable Device

As mentioned above, some implantable devices may have depots formed in a surface thereof, e.g., Figures 2B and 2C. In such embodiments, it may be desired to load particles 30 solely within the depots 28 of outer surface 20 of implantable device 10. Other than cleaning, implantable device 10 typically requires no particular surface treatment to retain particles 30 within depots 28.

The number of particles 30 loaded into depots 28 may be controlled by controlling parameters such as, but not limited to, the pressure with which particles 30 are projected from particle source 36, the angle θ of particle source 36 relative to depot 28, the distance d_{psos} between particle source 36 and depot 28, the ratio of therapeutic substance to filler within particles 30, and the actual size of particles 30. The number of particles 30 that will fit into any given depot 28 is primarily a function of the size of particles 30. Generally, larger particles 30 do not pack together within a defined space as easily as smaller particles 30 do. As the size of particles 30 increases, more empty spaces are created within depot 28 in between particles 30. By contrast, smaller particles 30 can pack together more readily, thereby allowing more particles 30 to be loaded into depot 28.

Figure 7A depicts a portion of implantable device 10 that contains depot 28 within outer surface 20 and has been loaded with particles 30 as described above. During the process, some particles 30 enter depot 28 while other particles 30 may be deposited along surface 20. Particles 30 located on outer surface 20 but not within depot 28 may be removed to yield implantable device 10 having particles 30 loaded solely in depot 28 as depicted in Figure 7B.

Particles 30 may be removed from outer surface 20 using conventional techniques, such as, but not limited to, scraping, squeegeeing, or soaking. The scraping method involves the mechanical stripping of particles 30 from outer surface 20 using, for example, a brush. The squeegeeing method involves passing implantable device 10 through an opening in a sponge filled with cleaning solution containing liquids such as, but not limited to, water, ethanol, DMSO, or hexane. The soaking method involves soaking implantable device 10 in a cleaning

Figure 9A illustrates an embodiment in which polymeric topcoat 42 is applied and dried subsequent to the loading of particles 30 onto outer surface 20 of primered implantable device 10. Such an embodiment facilitates immobilization of particles 30 on outer surface 20 via primer 38 followed by the controlled release of the substance or substances of which particles 30 are made via topcoat 42.

Figures 9B, 9C, and 9D illustrate alternative embodiments in which topcoat 42 is applied to implantable device 10 having depots 28 formed therein. In Figure 9B, topcoat 42 is applied over particles 30 within depot 28. In Figure 9C, topcoat 42 is applied along outer surface 20, which has no particles 30 loaded thereon, as well as over particles 30 within depot 28. In Figure 9D, topcoat 42 is applied over particles 30 within depot 28 and over particles 30 along primered outer surface 20.

Methods of Use

As mentioned above, implantable devices that may be treated according to the methods of the present invention include stents and grafts, among other possibilities. An implanted stent or graft, having one or more substances loaded thereon as described above, is useful for treating occluded regions of blood vessels caused by thrombosis and/or restenosis, among other possible uses.

Stents may be placed in a wide array of blood vessels, both arteries and veins. Briefly, an angiography is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by using a catheter to inject a radiopaque contrasting agent into an artery or vein as an X-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described covering may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

CLAIMS

What is claimed is:

1. A method of loading a therapeutic substance onto an implantable device, said method comprising:

projecting a dry stream of particles from a pressurized particle source onto a preselected region of said implantable device, said particles including a therapeutic substance.

2. An implantable device loaded with a therapeutic substance in accordance with the method of Claim 1.

3. The method of Claim 1, wherein said implantable device 10 is selected from a group of stents and grafts.

4. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof.

5. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of radioactive isotopes and radiopaque substances.

6. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of bioabsorbable polymers, biomolecules, and biostable polymers.

14. The method of Claim 13, wherein said particles are projected so as to become embedded within said polymeric primer.

15. The method of Claim 1, the method further comprising:

applying a polymeric topcoat disposed on at least a portion of said particles on said preselected region of said implantable device.

16. A method of loading a therapeutic substance onto a stent having an outer surface having a plurality of depots formed therein, said method comprising:

projecting a dry stream of particles from a pressurized source onto said outer surface of said stent, so that said particles are loaded into said plurality of depots, said particles including a therapeutic substance.

17. A stent loaded with a therapeutic substance in accordance with the method of Claim 16.

18. The method of Claim 17, wherein said particles are projected so as to be loaded onto said outer surface.

19. The method of Claim 18, additionally comprising the act of:

removing said particles from said outer surface of said stent, wherein said particles remain within said plurality of depots.

20. The method of Claim 18, wherein prior to said act of projecting particles, the method further comprises the act of:

applying a polymeric primer to said outer surface and within said depot, wherein said particles are retained on said primer following said act of projecting particles.

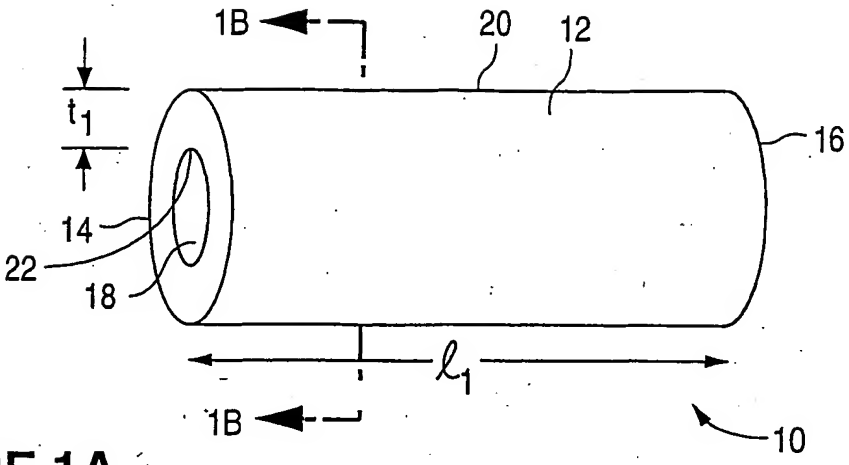

FIGURE 1A

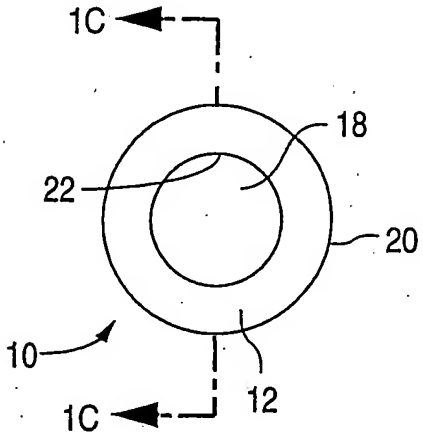

FIGURE 1B

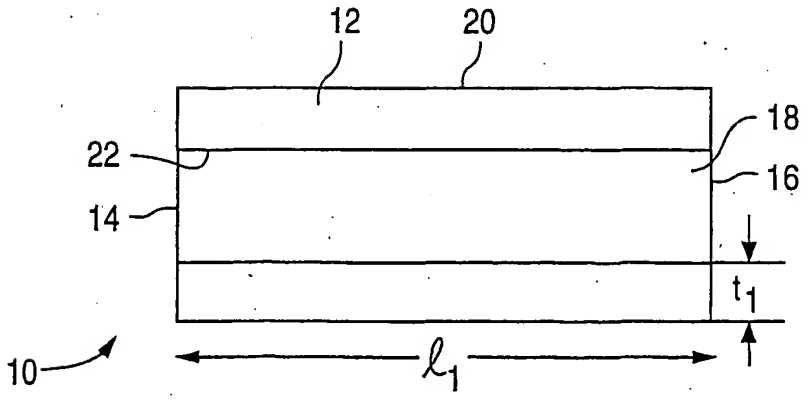

FIGURE 1C

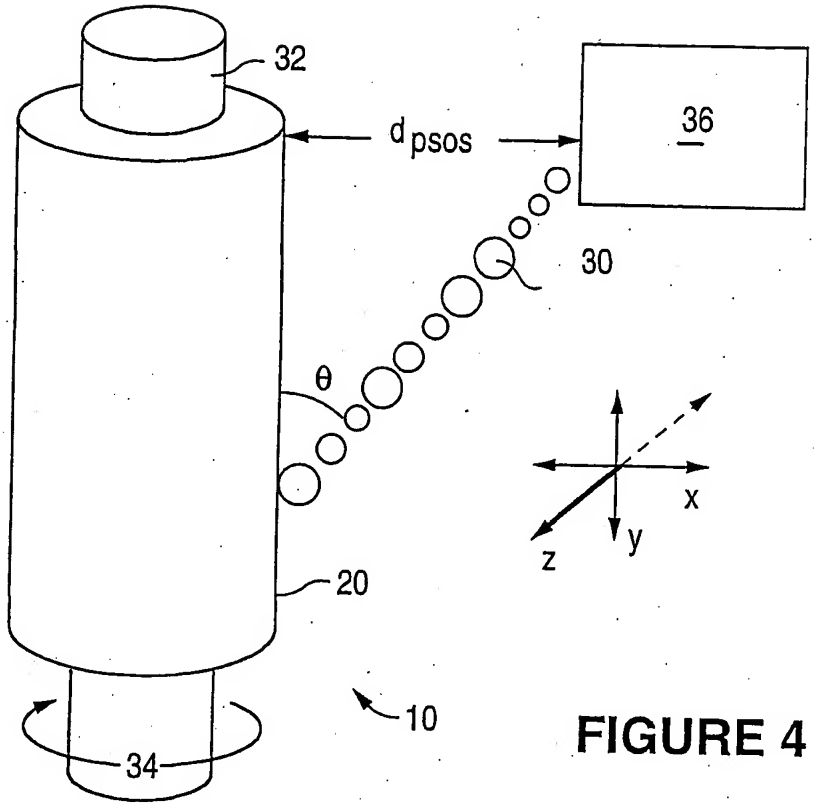

FIGURE 4

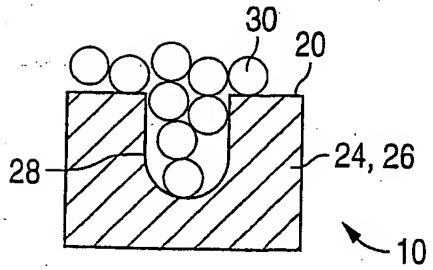

FIGURE 7A

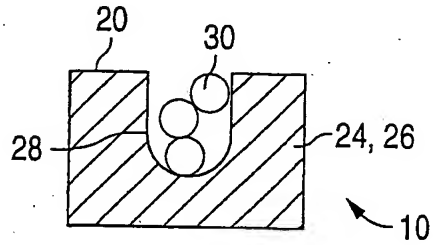

FIGURE 7B

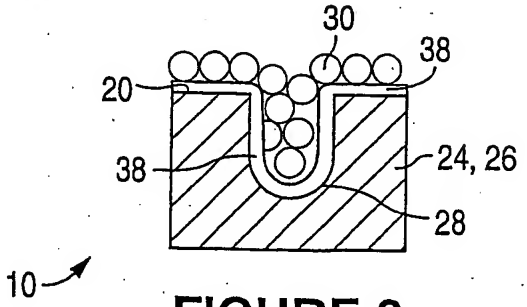

FIGURE 8

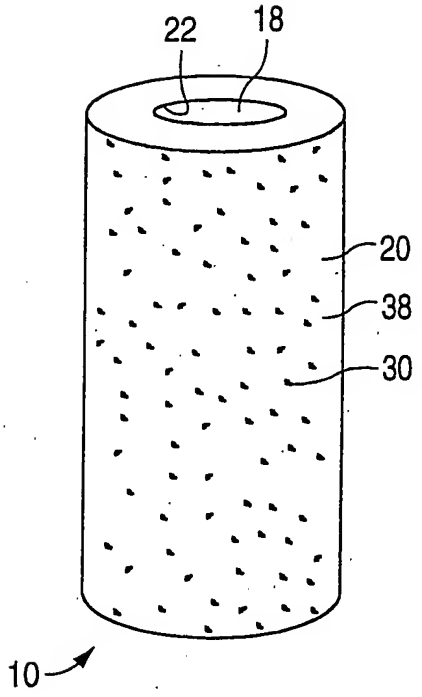

FIGURE 6A

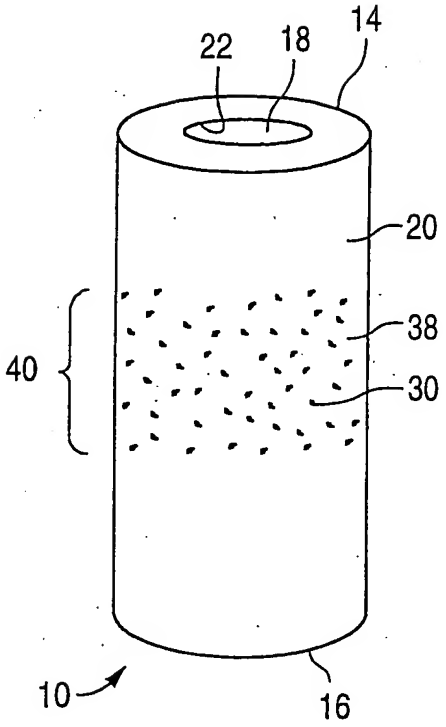

FIGURE 6B

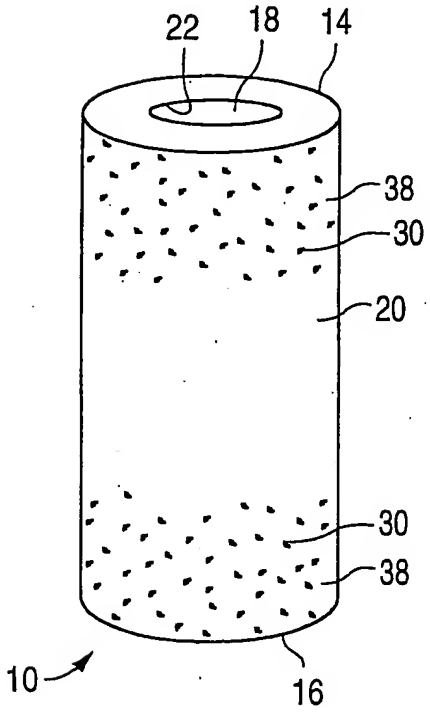

FIGURE 6C